Efficacy of GLP-1 Receptor Agonists (E.G., Semaglutide) In Non-Diabetic Obesity Management

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Abstract

The problem of obesity has now been recognized as one of the most important problems in the world. There has been an alarming rise in the incidence of obesity, which has also caused morbidity and mortality. Various health hazards of obesity include cardiovascular disease, metabolic disease, and cancer. It is accepted that lifestyle modification is an important factor in the management of obesity. However, it is difficult to achieve long-term management of obesity. This has necessitated the pharmacological management of obesity.

Currently, there are a number of persons who understand that there is a potential for a new way of treating obesity by utilizing glucagon-like peptide-1 receptor agonists. Although most of these medications were developed for the purpose of treating type 2 diabetes, they have also shown that they can be used for the purpose of treating obesity. It is believed that semaglutide is the most potent of all the GLP-1 modulators, as it not only slows down the rate of gastric emptying but also suppresses appetite and induces society

Substantial weight loss in body weight, body mass index, and waist circumference has also been reported in nondiabetic patients in recent clinical trials of semaglutide treatment versus placebo.Aside from weight loss, there are reports that improvements in other aspects of cardiometabolic risk factors are also seen. The safety profile of the drug is also acceptable. The most common adverse effects experienced by the patient are gastrointestinal upsets such as nausea and vomiting.

Keywords

Obesity; GLP-1 receptor agonists; Semaglutide; Weight loss; Non-diabetic; Pharmacotherapy

Introduction

It is defined by the measurement of body mass index, which is ≥30kg/m². It has been observed in the past few decades that the number of cases of obesity is increasing manifold in the world. It is an emerging health issue. According to the World Health Organization, almost three times the number of people are suffering from obesity compared to 1975. All age groups and socioeconomic classes are equally affected.[1]

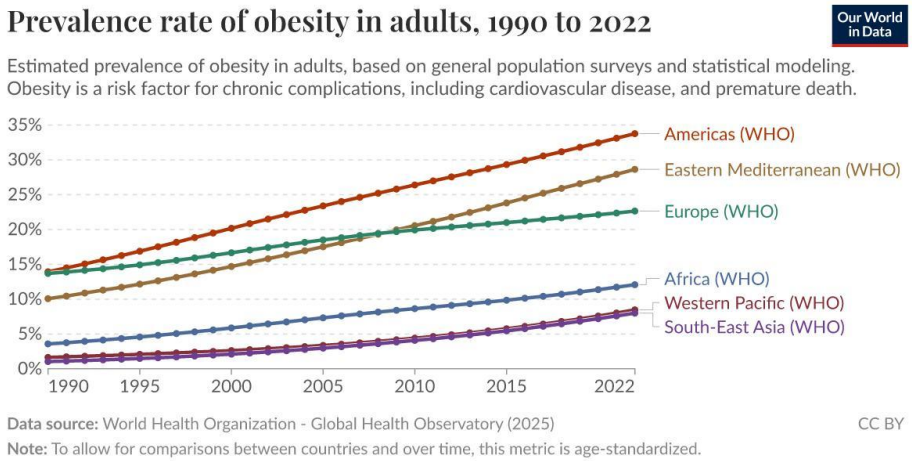


Figure 1: Global Obesity Trend

It is also related to other serious health problems, such as cardiovascular diseases, hypertension, diabetes mellitus type 2, cancer, etc. Moreover, the quality of life and the costs of healthcare are also affected. The factors which cause the occurrence of obesity are of multifactorial nature and include the balance of expenditure and intake of energy, genetics, environment, and behavior[2]

Modifications in lifestyle, which include changes in diet and exercise, are recommended. It is extremely difficult to achieve weight loss with modifications in lifestyle. For example, there is an increase in appetite, coupled with a decrease in energy expenditure in the body. Thus, there is an increased necessity for pharmacological agents in weight loss management [3]

Recently, there was an identification of a new category of drugs that is deemed effective in the management of obesity. The category of drugs that is deemed effective in the management of obesity is glucagon-like peptide-1 receptor agonists. The drug that is deemed effective in the management of weight loss in the absence of diabetes is recognized as belonging to the category of drugs deemed effective in the management of weight loss. The role in weight loss by reducing appetite, rate of stomach emptying, and feeling full is significant[4]

The aim of this review is to determine the effectiveness of GLP-1 receptor agonists, such as semaglutide, in the treatment of obesity among non-diabetic patients and the benefits and safety of the drugs in the prevention and treatment of obesity.

Pathophysiology of Obesity

It is a chronic complex multifactorial disorder that is linked with an excessive amount of adipose tissue that has negative effects on health. It is the state of imbalance that is in association with an excess of energy intake in comparison with the body’s energy expenditure, leading to the accumulation of fat. However, it is a complex state that is in association with the interplay of various factors. The central nervous system that comprises the hypothalamus is an important element in the maintenance of balance via the mediation of hunger and satiety[5]

The hypothalamus has neurons that regulate satiety and hunger. The orexigenic neurons regulate the feeling of hunger, while the anorexigenic neurons regulate satiety. The hormones that regulate satiety and hunger include hormones such as leptin and ghrelin. The hormone that regulates satiety is produced in the adipose tissue. The hormone is used in the regulation of food intake. The hormone that regulates hunger is produced in the stomach. The hormone is used in the regulation of food intake. The body of the obese person is resistant to the hormone that regulates satiety. Therefore, the body cannot regulate weight gain despite the availability of the hormone that regulates satiety [6]

Another role of insulin is the regulation of metabolism and the storage of fats. Insulin resistance is also common in obesity. This is the state where the body's cells are less responsive to insulin. This state leads to the impaired uptake of glucose, which in turn leads to high blood glucose levels and the storage of fats. The co-existence of insulin resistance in obesity leads to the occurrence of metabolic abnormalities, which may lead to type 2 diabetes and cardiovascular problems [7]

It is also now believed that adipose tissue is an endocrine organ that secretes different bioactive molecules that are referred to as adipokines. During obesity, the secretion of pro-inflammatory cytokines, which include tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), is elevated and is believed to be the major cause of the occurrence of insulin resistance and other complications of obesity, which include metabolic syndrome and cardiovascular diseases [8]

In addition, changes in hormones of the gut and signals from the gastrointestinal tract are also an essential factor in the pathophysiology of obesity. These hormones include GLP-1, peptide YY, and cholecystokinin. These

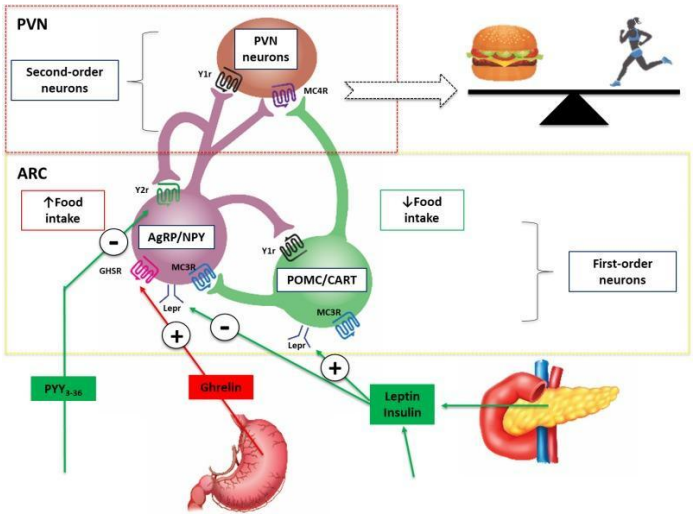


Figure 2: Pathophysiology of Obesity

hormones are of critical importance in the regulation of satiety and hunger. These signals can be altered in an obese individual, leading to hunger and satiety. Moreover, the current evidence also suggests that microbes in the gut are associated with fat storage, leading to obesity [9]

Mechanism of Action of GLP-1 Receptor Agonists

Glucagon-like peptide-1 is a hormone that is a part of incretin. It is released as a result of the intake of food. The synthesis of this hormone occurs through the action of L-cells in the intestine. The regulation of glucose and appetite occurs through this hormone. The inactivation of this hormone occurs through the action of DPP-4. The half-life of this hormone is very low. The agonists of this hormone are man-made[5]

Table 2: Mechanism of Action Summary

Mechanism	Effect
Appetite suppression	Reduced calorie intake
Gastric emptying delay	Increased satiety
Insulin secretion	Improved glucose control
CNS reward modulation	Reduced food cravings

This category of drugs, such as Semaglutide and Liraglutide, have different mechanisms of action. One of the ways that this category of drugs works is that they suppress appetite through the hypothalamus. This category of drugs works by suppressing appetite or satiety through the GLP-1 receptor in the hypothalamus, leading to a reduction in caloric intake and consequently leading to weight loss[7]

Further, the GLP-1 receptor agonists slow the rate of emptying of the stomach. Consequently, this slows the time of fullness after the meal. This action of the agonists contributes to the weight loss action of the agonists. Lastly, the agonists stimulate insulin in direct proportion to the blood glucose levels. This action maintains metabolic equilibrium with little risk of hypoglycemia[6]

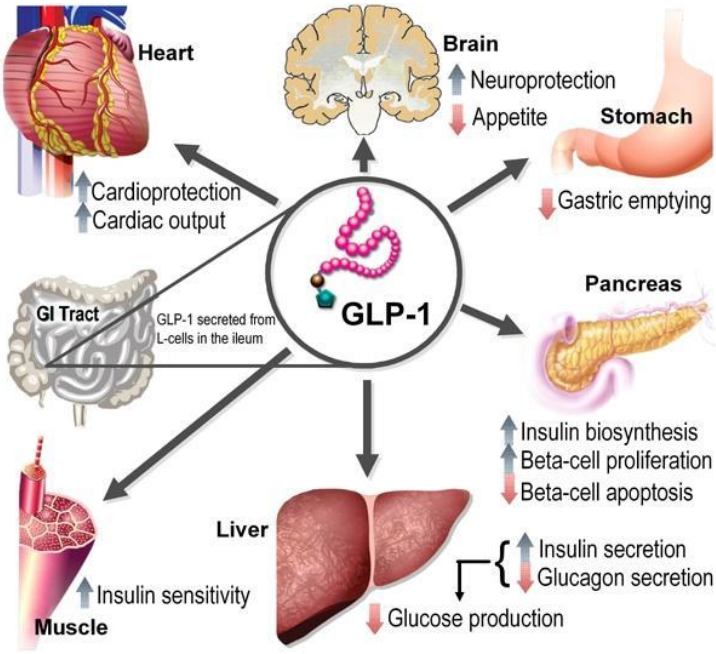


Figure 3: Mechanism of GLP-1 Receptor Agonists

In addition, it is recognized that there is an action of the GLP-1 agonists on pathways in the brain, which are associated with reward. These include those associated with food, as well as those associated with pleasure. These are all key factors in the development of obesity. New research findings have also shown the beneficial effects of the GLP-1 agonists on cardiovascular parameters, including lowering of blood pressure, lipid profiles, as well as inflammation[7]

Overall, the mechanisms of action of GLP-1 R agonists for appetite suppression, gastric emptying, improved insulin secretion, and reward modulation in the CNS make them potent weight loss agents. Moreover, GLP-1 R agonists have also been observed to be effective in non-diabetic patients, irrespective of their hypoglycemic effects[6], [9]

Pharmacology of GLP-1 Receptor Agonists with Special Reference to Semaglutide

Therefore, it can be stated that the role of glucagon-like peptide-1 receptor agonists can be considered as an advancement in the management of obesity, especially in the case of nondiabetic obese patients. As discussed in the above paragraphs, it is evident that the role of the hormone, i.e., glucagon-like peptide-1, in glucose metabolism and weight is well documented. However, it is evident that the activity of the hormone is impaired. This is due to the fact that the half-life of the hormone is extremely low, i.e., only 1-2 minutes. In addition, it is evident that the hormone gets inactivated extremely quickly through an enzyme, which is known by the name of dipeptidyl peptidase-4. Long-acting glucagon-like peptide-1 receptor agonists are developed by modifying the structure of the hormone in such a manner that it is resistant to inactivation by the enzyme DPP-4[10]

Among all the agonists of the GLP-1 receptor developed and commercialized thus far, Semaglutide has been identified as the most potent in managing the condition of obesity. The structural composition of Semaglutide is almost identical to that of the natural form of GLP-1, except for some modifications in the amino acids, which

enable it to reversibly associate with albumin. This enables it to be protected from inactivation by DPP-4, in addition to increasing its half-life to a week, thus enabling it to be administered once a week, as opposed to the other agonists of the GLP-1 receptor, which are to be administered once a day [11]

Table 3: Pharmacokinetic Profile of Semaglutide

Parameter	**Value**
Half-life	~168 hours
Administration	Subcutaneous / Oral
Dosing frequency	Weekly
Metabolism	Proteolytic degradation
Bioavailability	High (SC), Low (oral)

From the pharmacodynamic perspective, the effect of semaglutide is that it binds with the GLP-1 receptors in the body parts such as the pancreas, central nervous system, gastrointestinal system, and cardiovascular system. The binding of semaglutide with the GLP-1 receptors in the pancreas results in the glucose-dependent secretion of insulin in the body. Also, it inhibits the secretion of glucagon in the pancreas. The effect of semaglutide is beneficial in the sense that there is no possibility of the onset of hypoglycemia since the glucose is secreted in the presence of high levels of glucose. The effect of semaglutide is beneficial not only in the case of diabetic patients but also in the case of non-diabetic obese patients[12]

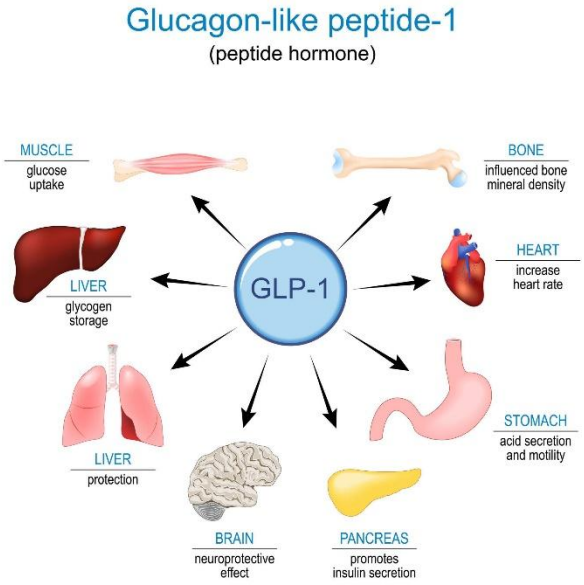


Figure 4: Semaglutide Pharmacokinetics & Action Sites

One of the most important pharmacological effects of semaglutide, especially in relation to its effect on obesity, is that it crosses the blood-brain barrier and stimulates the GLP-1 receptor in the hypothalamus. The hypothalamus is the most important part of the brain in relation to hunger. The stimulation of this receptor leads to a reduction in hunger and a feeling of satiety. This leads to a reduction in the number of calories consumed, and this effect probably represents the most important effect of the drug in relation to weight loss. The drug also stimulates the mesolimbic reward system, leading to a reduction in the hedonic effects of food[13]

Another significant pharmacological effect of semaglutide is the slowing of gastric emptying. This slowing of the rate of digestion of food and the time taken for the food to be passed from the stomach into the intestine helps in increasing the feeling of fullness after the meal. This helps in controlling the food taken and also in controlling the blood glucose levels. However, this effect of slowing the rate of gastric emptying is reduced, but the effect of controlling the food taken is long-lasting and helps in losing weight [12]

The pharmacokinetic profile of the drug semaglutide may be defined as follows: This drug, if taken subcutaneously, has a high bioavailability rate. This is because the half-life of the drug is 168 hours, which implies that the drug is taken once a week. This is the positive aspect of the drug in relation to compliance. This drug binds very well to the plasma albumin of the human body. This is helpful in evading the clearance of the drug by the kidneys and the liver. This drug is metabolized through proteolytic cleavage and the beta-oxidation of the fatty acid side chain. However, the cytochrome P450 enzyme is not involved in the metabolism of the drug [14]

Apart from that, there is also the oral form of the drug. This form of the drug could be said to be a breakthrough in the administration of peptide drugs. This is because it is co-formulated with an absorption enhancer, which is also known as sodium N-(8-[2-hydroxybenzoyl]amino) caprylate. This is abbreviated as SNAC. This ensures that the drug is absorbed by the gastric epithelium. Even though it is said that the drug is of low bioavailability, the drug is available for those who prefer the oral form of the drug [12]

Additionally, clinical trials have shown that semaglutide leads to weight loss among people who are suffering from obesity, including those who are not suffering from diabetes. The weight loss effect of semaglutide is greatly pronounced compared to the weight loss effect of the previously used drugs against obesity. This makes the drug one of the most effective in the treatment of obesity. This drug not only leads to weight loss but also improves body composition through the reduction of visceral fat, which is closely related to the risk factors. [13]

Apart from the reduction of weight loss, it has been proved that semaglutide has some positive effects on the body. The positive effects of semaglutide on the body include the reduction of blood pressure. It also helps in the improvement of lipid metabolism by reducing low-density lipoproteins and triglycerides. In addition, it helps in the reduction of inflammation. This is important since it helps in the reduction of cardiovascular diseases. Cardiovascular diseases are linked to obesity. [14]

Despite the fact that there are some advantages associated with the drug, there are also some side effects associated with the drug. The side effects associated with the drug have different natures, but most of them are associated with the gastrointestinal type. Some of the side effects associated with the drug include nausea, vomiting, diarrhea, and constipation. These side effects occur in the early stages of the administration of the drug in the body. The side effects associated with the drug have mild or moderate natures but tend to diminish with time as the body gets used to the drug. The drug also has some other side effects, which include pancreatitis, gallbladder disease, and medullary thyroid carcinoma, although in animal models [10]

Another important factor which needs to be taken into consideration in the pharmacological use of the drug is the issue of weight relapse in the case of discontinuation of the drug. It has been observed that in the case of discontinuation of the drug, there is a relapse of the lost weight, which means that the drug needs to be taken for a long time, if not for a lifetime, in order to maintain the efficacy of the drug. This means that obesity is a chronic condition [15]

Another limitation of this drug is the cost and accessibility. This limitation is also linked to the semaglutide therapy. The cost of the therapy may be another limitation that may affect the usage of the drug. The long-term use of the drug may also be another limitation in the future, considering the cost. There are already efforts to make the drug more affordable and explore alternative drugs [16]

When it was compared with other agonists for GLP-1, like Liraglutide, it was found that semaglutide was effective in reducing weight and was also easy to use due to the dosing regimen. For liraglutide, it is necessary to take it daily. However, semaglutide is to be taken once a week, and this makes it easy for patients to comply with and be satisfied with taking the drug. During clinical trials, it was also found that there was a greater reduction in weight due to semaglutide in comparison to liraglutide. [13]

It can, therefore, be concluded that the pharmacological profile of the drug enhances the efficacy of the drug as an all-encompassing therapy for the management of obesity. The potential of the drug in modulating various physiological pathways in the regulation of energy homeostasis, appetite, and metabolism further confirms that

the drug is a highly prized therapy in the management of obesity. With the ever-increasing research in this field, it can be anticipated that in the future, semaglutide, along with other GLP-1 RA drugs, would be at the helm in the management of obesity, especially in non-diabetic patients.

Overview of GLP-1 Receptor Agonists

One such class of incretin-based drugs that is known to have a significant impact on the pharmacological management of obesity and metabolic disorders is the glucagon-like peptide-1 receptor agonists. It is known that the glucagon-like peptide-1 receptor agonists have the physiological activity of the endogenous incretin hormone GLP-1, which is released from the intestinal L-cells in response to food intake. The incretin hormone GLP-1 has been known to play a significant role in the regulation of glucose metabolism and food intake by stimulating insulin secretion, inhibiting glucagon secretion, delaying gastric emptying, and reducing food intake. The half-life of the incretin hormone GLP-1 has been known to be very short due to its rapid degradation by the enzyme dipeptidyl peptidase-4. In order to overcome the limitation of the short half-life of the incretin hormone GLP-1, the glucagon-like peptide-1 receptor agonists have been developed [17]

The two classes of GLP-1 receptor agonists are as follows: short-acting GLP-1 receptor agonists, like exenatide, can be used to control blood sugar levels by reducing the rate at which food passes through the stomach and enters the bloodstream. Long-acting GLP-1 receptor agonists that can be used to control weight loss include semaglutide and liraglutide. This class of medications can help patients with diabetes control their blood glucose levels in addition to aiding non-diabetic individuals in losing weight [18], [19]

Table 1: Classification of GLP-1 Receptor Agonists

Class	**Drug**	**Duration**	**Dosing**
Short-acting	Exenatide	Short	Twice daily
Long-acting	Liraglutide	Medium	Once daily
Long-acting	Semaglutide	Long	Once weekly

The drug, semaglutide, is a GLP-1 receptor agonist with a long half-life, and it has been given a lot of attention because of its increased efficacy and mode of administration. The drug has been made resistant to inactivation by DPP-4 enzymes and binds to albumin in the blood, giving it a long half-life of a week. From the clinical trials, it is evident that semaglutide leads to a significant weight loss, decrease in body mass index, and decrease in waistlines.The mode of action of semaglutide includes its effect on appetite through the central nervous system, delayed gastric emptying, and reduced caloric consumption. [20]

Liraglutide, another significant GLP-1 receptor agonist, requires once-daily subcutaneous injections due to its 13-hour half-life. Furthermore, higher doses of Liraglutide than those used to treat diabetes are approved for the treatment of chronic weight. Liraglutide and semaglutide have similar pharmacological effects, including decreased appetite, enhanced satiety, and enhanced metabolic function. The once-daily dosage, as opposed to the once-weekly dosing with semaglutide, has an effect on medication compliance despite its effectiveness [21]

The pharmacokinetics of GLP-1 receptor agonists differ based on the structure of the drug. GLP-1 receptor agonists are designed in a way that they have a longer half-life and are degraded by fewer enzymes. The long-lasting effect of semaglutide is due to the binding of the drug to albumin, which increases the effect of the drug by slowing down its clearance rate. Most GLP-1 receptor agonists are given by injection in a way that they maintain the level of absorption. Within the last few years, the oral form of semaglutide has been developed by using absorption enhancers in patients who do not wish to use injections. [22]

The pharmacodynamics of GLP-1 receptor agonists is beneficial in controlling weight loss and metabolism. The mechanism of action of GLP-1 receptor agonists in controlling glucose metabolism is through the reduction of

the level of glucagon and the promotion of the release of insulin in a glucose-dependent manner. The other benefit of GLP-1 receptor agonists is in the control of the fullness feeling after eating through the delay in the emptying of the stomach. The other benefit of GLP-1 receptor agonists is that they have the advantage of reducing food intake through the reduction of the level of appetite and fullness through the stimulation of the hypothalamus in the central nervous system. The GLP-1 receptor agonists are very potent in controlling obesity due to their effects, which result in weight loss. [17]

With regard to the dosage and administration of these drugs, GLP-1 receptor agonists are titrated up gradually to the target dose from a low dose. Semaglutide is titrated up gradually to the target dose from a low weekly dose to a dose of 2.4 mg once weekly for the treatment of obesity. Liraglutide is titrated up gradually to the target dose from a low dose by increments to a dose of 3.0 mg/d. The gradual increment of the dose of these drugs helps in the improvement of the tolerability of these drugs by reducing the side effects of these drugs, which include nausea and vomiting. The drug and the dosage form selected is based on several factors in individual patients, which include tolerance, patient preference, cost, and efficacy[23]

Thus, the role of GLP-1 receptor agonists can be considered a highly potent and versatile drug in the management of obesity. The potential of these drugs to influence multiple physiological pathways in obesity has made them an important drug in this area. Among these, semaglutide and liraglutide have been identified to be important drugs in this class, which have established their efficacy, safety, and benefits in the management of obesity. With the progress of further studies, these drugs can be considered to play an important role in the management of obesity, especially in non-diabetic patients.

Clinical Efficacy of GLP-1 Receptor Agonists in Non-Diabetic Obesity

1 Overview of Clinical Evidence

The GLP-1 receptor agonists have shown promising efficacy in the management of obesity, especially in patients who are not diabetic. The efficacy of GLP-1 receptor agonists has already been tested in RCTs, which have shown promising results in the management of obesity. Among the GLP-1 receptor agonists, Semaglutide is the drug which has shown promising efficacy in the management of obesity, as it has shown more promising results in the management of obesity than the previously used pharmacological agents in the management of obesity. The advantages of using GLP-1 receptor agonists can be regarded as a major advancement in the management of obesity [20]

2 STEP Clinical Trial Program

The clinical trial program for the Semaglutide Treatment Effect in People with Obesity, also known as the STEP clinical trial program, is a group of phase 3 clinical trials aimed at assessing the efficacy and safety of semaglutide in non-diabetic overweight or obese subjects. The STEP 1 clinical trial showed that subjects who were subjected to semaglutide 2.4 mg once a week resulted in a weight loss of 14.9% on average compared to 2.4% for placebo subjects, thus proving the efficacy of semaglutide over lifestyle modifications. The STEP 3 clinical trial has shown better weight reduction results for subjects treated with semaglutide in combination with intensive behavioral therapy. The STEP 4 clinical trial has shown that therapy should continue in order to achieve weight reduction results, as weight gain is observed when semaglutide is discontinued. [13], [24]

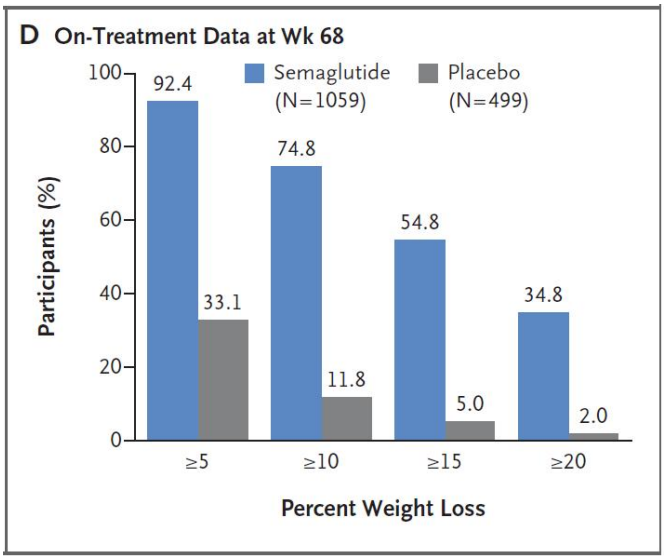


Figure 5: STEP Trial Weight Loss Results

3 Weight Loss Outcomes

Significant weight loss in terms of total body weight has also been observed in the clinical studies performed on GLP-1 receptor agonists. In fact, a significant number of patients have been observed to experience weight loss when they are subjected to semaglutide therapy. This includes a significant number of patients who experience weight loss to the extent of 5%, 10%, and even 15% or more of their original weight. Apart from the weight loss experienced by the patients with regard to the total body weight, some studies also observe that the patients experience a significant weight loss with regard to the BMI as well as the waist and visceral fat. This is indeed a significant finding with regard to the weight loss experienced by the patients with regard to the visceral fat, as this is one of the major risk factors for cardiometabolic diseases. The weight loss experienced by the patients who are subjected to semaglutide therapy is indeed significant compared to the other anti-obesity drugs. [13]

4 Comparison with Other GLP-1 Receptor Agonists

Other GLP-1 receptor agonists, such as Liraglutide, have also demonstrated potential in the management of non-diabetic obese patients, although to a lesser extent than semaglutide. Research studies have revealed that liraglutide has resulted in a reduction in weight loss of 5-8% of a patient's body weight on average. Although this is significant, semaglutide has demonstrated better results due to its long half-life and potency, which enable a patient to take a dose on a weekly basis to enhance compliance with the drug. This demonstrates the advancement of new GLP-1 receptor agonists in managing obese patients through weight loss results [21]

5 Cardiometabolic Benefits

However, apart from the reduction in weight, other significant advantages of GLP-1 receptor agonists, apart from the treatment of obesity, are the improvement in the patient’s cardiometabolic risk factors. For example, it has been established through clinical studies that the use of GLP-1 receptor agonists is associated with a reduction in both systolic and diastolic blood pressure, as well as a reduction in lipid profiles, which include a reduction in LDL cholesterol and a rise in HDL cholesterol, as well as a reduction in inflammation. The improvement in the patient’s risk factors for heart diseases, which are associated with obesity, further emphasizes the importance of GLP-1 receptor agonists. [16]

6 Safety and Tolerability

It has been observed that these GLP-1 receptor agonists have a good safety profile; therefore, these drugs can be used in the long term. It has been observed that these drugs have side effects related to the gastrointestinal system. The side effects of these drugs include nausea, vomiting, and diarrhea. It has been observed that these side effects

decrease as time progresses because the body gets adapted to these drugs. It has also been observed that these drugs are safe in non-diabetic patients due to the risk of hypoglycemia because these drugs act on glucose levels. Therefore, the safety profile of these drugs has made these drugs popular in the treatment of obesity. [15]

7 Sustainability of Weight Loss

The other important aspect to consider in the evaluation of the clinical efficacy of GLP-1 receptor agonists in the treatment of obesity is the maintenance of weight loss. From the evidence derived from the clinical trial data, it is evident that the maintenance of the therapeutic response of the drug is based on the continued use of the drug. This is because, when the drug therapy is stopped, there is a return to the initial weight, which demonstrates a chronic and relapsing nature of obesity. Therefore, from the evidence, it is evident that long-term pharmacotherapy for obesity is essential for the maintenance of weight loss [24]

8 Overall Clinical Significance

It can, therefore, be concluded that GLP-1 receptor agonists are a highly effective and innovative method of managing obesity in non-diabetic patients. The effectiveness of GLP-1 receptor agonists in inducing weight loss, improving metabolic parameters, and having a positive safety profile makes these drugs superior to traditional anti-obesity drugs. Amongst all GLP-1 receptor agonists, semaglutide has been identified as a highly effective drug in managing obesity in patients. Therefore, with more studies being conducted on their long-term effects and potential in combination therapy, GLP-1 receptor agonists will always be at the forefront in managing obesity in patients.

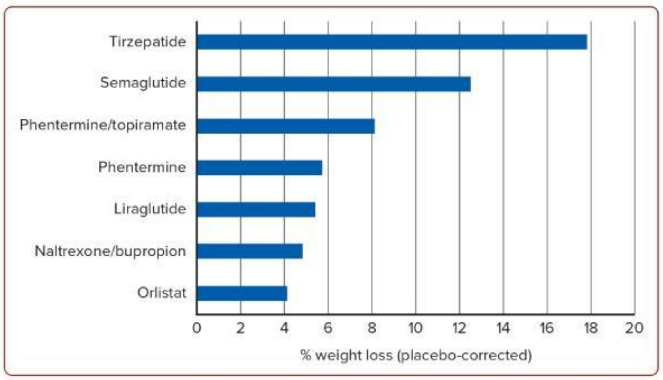
Comparison with Other Anti-Obesity Drugs

1 Traditional Anti-Obesity Drugs vs GLP-1 Receptor Agonists

Traditionally, anti-obesity medications have been used in combination with lifestyle modifications for weight management. However, these medications have shown limited efficacy in weight management. Orlistat and sympathomimetics have shown limited efficacy in weight management, as these medications work through a single target, fat absorption, and appetite reduction, respectively. On the other hand, GLP-1 receptor agonists have shown a holistic mode of action in weight management by inhibiting multiple targets, such as appetite reduction, delay in gastric emptying, and improvement in metabolic functions. Medications such as Semaglutide have shown significant efficacy in weight management by inhibiting these targets. Therefore, it can be concluded that the mode of action of GLP-1 receptor agonists has a definite advantage over other anti-obesity medications. [26].

2 Efficacy and Sustainability of Weight Loss

One of the main drawbacks of the current anti-obesity medications is their efficacy and inability to sustain the effects over time. Generally, the current medications can reduce weight by an average of 3 to 8 percent of the original body weight. It is believed that this might not be sufficient for individuals with severe obesity. Moreover, the effect is reversed when the medications are stopped. GLP-1 receptor agonists, including semaglutide, have been shown to reduce weight to a much greater extent, with reductions exceeding 10 to 15 percent of the original



Data sources: Jastreboff et al.[75] (tirzepatide); Wilding et al.[69] (semaglutide); Gadde et al.[62] (phentermine/topiramate); Aronne et al.[59] (phentermine); Pi-Sunyer et al.[66] (liraglutide); Greenway et al.[65] (naltrexone/bupropion); Sjöström et al.[63] (orlistat).

Figure 6: Comparison of Anti-Obesity Drugs

body weight. Moreover, the medications can sustain the effect because they directly affect the appetite control centers and the behavioral aspects of eating. [21], [27].

3 Comparison with Orlistat

One of the most popularly used anti-obesity medications is Orlistat, which is also considered to be the first medication of its kind. Orlistat acts by inhibiting the activity of pancreatic lipases, which results in the loss of 30 percent fat. Even though this results in the loss of 3 to 5 percent of the original body weight, this is not accompanied by the reduction in appetite and increase in energy expenditure. It can therefore not be considered to be as effective as GLP-1 receptor agonists in the treatment of obesity. Furthermore, Orlistat is also associated with gastrointestinal side effects such as oily stools, flatulence, and fecal urgency. GLP-1 receptor agonists not only cause greater weight loss but also improve health outcomes in general [26].

4 Comparison with Phentermine–Topiramate

Phentermine-Topiramate is a dual-action drug, which means that it consists of two drugs, namely an anticonvulsant drug and a sympathomimetic appetite suppressant drug. It has been proved that the drug results in more weight loss compared to other drugs. The average weight loss varies from 8 to 10 percent of the original weight. However, the drug results in some possible side effects, which include tachycardia, sleep problems, mood problems, and cognitive problems. Moreover, the safety of the drug and the possible abuse of the drug by the patient during the course of treatment can be considered to be major drawbacks of the drug. The safety of the drug, namely GLP-1 receptor agonists, can be considered to be better compared to the dual-action drug, namely phentermine-topiramate, mainly because these drugs have no impact on the cardiovascular system. Moreover, it has been proved that semaglutide results in more weight loss compared to other drugs, making it the best drug for the treatment of obesity. [27].

5 Overall Comparison and Clinical Implications

On an overall level, it can be said that GLP-1 receptor agonists are a major improvement over traditional anti-obesity medications. The efficacy of these medications in weight loss is a major improvement over traditional medications. The additional benefits of these medications in terms of metabolic effects are a major advantage of these medications over traditional medications. Although there is some place for traditional medications such as orlistat and phenteramine-topiramate in clinical scenarios, these medications are less effective and have more drawbacks in terms of tolerability and efficacy. The introduction of GLP-1 receptor agonists, such as semaglutide, has revolutionized the management of obesity in a holistic manner. [21], [26].

Table 5: Comparison with Other Drugs

Drug	Weight Loss	Mechanism	Limitations
Orlistat	3–5%	Fat absorption inhibition	GI side effects
Phentermine-Topiramate	8–10%	Appetite suppression	CNS side effects
Semaglutide	10–15%+	Multi-target	Cost

Safety and Adverse Effects of GLP-1 Receptor Agonists

1 General Safety Profile

It has been proved that the administration of GLP-1 receptor agonists is safe and tolerable for the purpose of treating obesity, even in non-diabetic patients. The efficacy and safety of administration of GLP-1 receptor agonists for treating obesity have been proved through various studies conducted on patients. It has been proved that the side effects associated with the administration of GLP-1 receptor agonists are mild to moderate in nature,

and they can be overcome spontaneously with time as the body gets adapted to such medication. The best benefit-risk relationship for treating obesity is offered by the administration of GLP-1 receptor agonists such as Semaglutide. [12]

Table 6: Adverse Effects

Category	**Adverse Effects**
Gastrointestinal	Nausea, vomiting, diarrhea
Rare	Pancreatitis
Others	Gallstones, thyroid concerns

2 Gastrointestinal Adverse Effects

The most frequent side effects associated with the use of GLP-1 receptor agonists include gastrointestinal side effects such as nausea, vomiting, diarrhea, constipation, and abdominal pain. The most frequent side effects include nausea, especially when the medication is initiated or the dose is increased. The side effects are temporary. The side effects can be minimized by escalating the dose. The medication can be started with a low dose, and the dose escalated to enhance tolerability. [25]

3 Risk of Pancreatitis

Even though this is not a common occurrence, the GLP-1 receptor agonists have been associated with the occurrence of acute pancreatitis. Even though there is no concrete evidence, caution is needed when the patient is administered the drug if the patient has a history of pancreatitis. The patient is to be monitored in case acute pancreatitis occurs, as it is characterized by abdominal pain. [10]

4 Gallbladder-Related Disorders

The administration of these medications has been related to the development of gallbladder diseases such as cholelithiasis and cholecystitis. Rapid weight loss, which is a side effect of the administration of these medications, has been known to cause the development of gallstones. The patient is to be educated on the signs and symptoms of the complications that may arise in the gallbladder, such as abdominal pain and jaundice. Monitoring is to be done accordingly. [25]

5 Thyroid Safety Concerns

This risk is well understood with the use of GLP-1 receptor agonists in medullary carcinoma of the thyroid; however, little information is available on this in humans. These drugs must be contraindicated in patients with a history of medullary carcinoma of the thyroid and multiple endocrine neoplasia syndrome 2. The screening must be performed before the administration of the drug. [12]

6 Risk of Hypoglycemia

The risk is less in non-diabetic patients who are on the drug known as GLP-1 receptor agonists. The insulin is released only in hyperglycaemic conditions. If the patient is on other anti-diabetic drugs such as insulin and sulphonyl urea, then the risk is high. In non-diabetic patients who are on drugs known as GLP-1 receptor agonists for obesity, hypoglycaemia is not observed. [10]

7 Injection-Site Reactions and Administration Issues

With regard to subcutaneous injections, these medications can cause mild injection site effects, which include redness, swelling, or itching at the injection site. The occurrence of these effects does not warrant a change in these medications. The availability of an oral version of semaglutide offers a choice for patients who are averse to injectable medications. [25]

8 Long-Term Safety and Cardiovascular Effects

Not only do these studies prove that these drugs are safe for use, but they also prove that these drugs have a positive effect on the cardiovascular system of a patient. The positive effects of these drugs on the cardiovascular system include a reduction in blood pressure, a reduction in lipid levels, and a reduction in major adverse cardiovascular events. All these have a positive effect on the body of an obese patient who is at risk of suffering some adverse effects on his/her cardiovascular system. [10]

9 Limitations and Safety Considerations

Even though they have a safe profile, there are some disadvantages related to the use of these medications. The disadvantages of these medications are the cost of the drugs, the time required for the treatment, and the weight gain following the treatment. It is very important to select the patients in order to avoid any complications.

Benefits Beyond Weight Loss

1 Improved Metabolic Profile

Other than the obvious benefits in the context of weight loss, there are many other benefits in the context of metabolic health. GLP-1 RA is well known to improve glycemic control by increasing insulin levels and decreasing glucagon levels in a glucose-dependent manner, which is beneficial in maintaining blood glucose levels in both diabetic and non-diabetic patients. It is well known that GLP-1 RA improves lipid metabolism by decreasing the levels of total cholesterol, LDL, and triglycerides. It can also increase the level of HDL. All these benefits can help in achieving a healthy metabolic state, which in turn can help in the prevention of metabolic syndrome. It can also improve insulin sensitivity and decrease inflammation, which can help in the improvement of metabolic health[26]

2 Cardioprotective Effects

The cardioprotective properties associated with the GLP-1 receptor agonists have been quite remarkable, as these agents have been found to be the most effective in the prevention of cardiovascular diseases in patients who are at the risk of developing such diseases. The cardioprotective properties associated with these agents have already been proved through the clinical trials performed on patients, as these trials have found these agents to reduce the cardiovascular events, heart attacks, and strokes in the patients, especially those who are at the risk of developing such diseases. The cardioprotective properties associated with the GLP-1 receptor agonists have been found to be related to the improvements in the endothelial functions, hypertension, and systemic inflammation in the patients. The GLP-1 receptor agonists have been found to have effects on the cardiovascular system, irrespective of the weight loss, through the direct effects on the cardiovascular system, indicating the potential use of these agents in controlling the weight as well as in the prevention of heart diseases in the patients. [26]

3 Reduction in Liver Fat and Inflammation

The other important advantage of GLP-1 receptor agonists is that they have the potential to decrease the level of fat in the liver. Non-Alcoholic Fatty Liver Disease (NAFLD), which is mostly related to obesity, is a disease in which a high level of fat is accumulated in the liver. This disease has the potential to lead to a number of serious pathological conditions such as Non-Alcoholic SteatoHepatitis (NASH). GLP-1 receptor agonists have the potential to decrease the level of fat in the liver. GLP-1 receptor agonists have the potential to decrease the level of inflammation in the liver. This will be a great advantage to those suffering from obesity because NAFLD is mostly related to obesity. [10]

4 Potential Benefits in Cardiovascular and Neurological Conditions

Research has shown that current research suggests that other benefits can be obtained from these drugs, particularly in the management of neurological disorders. It has been found that these drugs have neuroprotective benefits, which can also include anti-inflammatory and antioxidant effects. It has been found that these drugs have shown benefits in terms of neuronal survival, which can help in reducing the risk of neurodegenerative diseases such as Alzheimer’s and Parkinson’s. Even though these studies are in the early stages, it is clear that these drugs can provide other benefits.

Moreover, the combined effects of improved metabolic health, reduced inflammation, and enhanced vascular function further support their role in preventing complications associated with both cardiovascular and neurological disorders. While more long-term clinical studies are needed to confirm these benefits, current evidence suggests that GLP-1 receptor agonists have a wide range of positive effects that extend beyond simple weight reduction [27]

5 Summary

In this regard, the summary of the benefits of GLP-1 receptor agonists shows that aside from the weight loss benefit, there are also other benefits, such as the favorable metabolic profile, cardioprotective effects, reduction in fat and inflammation in the liver, as well as the potential role in the prevention of other diseases such as cardiovascular and neurological diseases. In this regard, GLP-1 receptor agonists offer a holistic approach in the management of obesity and its related complications.

Limitations

1 Limitations of GLP-1 Receptor Agonists

Even though there is a high level of efficacy in the management of obesity with GLP-1 receptor agonists, there are a number of disadvantages associated with these drugs. One of the disadvantages associated with these drugs is their high cost. The use of these drugs may not be feasible in low- and middle-income societies due to their high cost. These drugs may have to be used over a long period of time, and in some cases, these drugs may have to be used over a lifelong period to ensure a high level of weight loss. Even though these drugs are highly effective in managing obesity, not all patients may respond to these drugs to a high level. There are variations in the level of response to these drugs, and some patients may respond to these drugs at a moderate level [28]

2 Adherence and Long-Term Use Challenges

It is difficult to adhere to GLP-1 receptor agonist therapy for a number of reasons, which include the frequent use of these medications, side effects of these medications, and high costs of these medications. Even though GLP-1 receptor agonist medications, which are taken on a weekly basis, such as Semaglutide, have been developed, which are less frequent than those taken on a daily basis, adherence to these medications over a period of time is a concern. In addition, gastrointestinal side effects of these medications, which are experienced in the initial stages of therapy, may also result in less adherence to these medications. Patient education and dose optimization of these medications are required to get maximum benefits from these medications [29]

3 Weight Regain After Discontinuation

The drawback of GLP-1 receptor agonists has also been identified to be the tendency to regain weight after the cessation of drug therapy. Clinical studies have shown that after the cessation of drug therapy, patients show the tendency to regain a large proportion of the weight lost. Again, this highlights the chronicity and tendency to relapse in obesity, where the patient is required to be on drug therapy to show weight loss. An important point is highlighted with this, which is the tendency to sustain the drug therapy [30]

4 Safety Concerns and Knowledge Gaps

Although these drugs have shown promise in terms of good tolerability, there is a need to obtain further information on the long-term safety of these drugs. There has been a concern raised on the possible occurrence of some rare side effects of these drugs, such as pancreatitis, gallbladder disease, and thyroid function. There is a need to obtain further information on the safety of these drugs for different groups of patients, such as elderly patients, pregnant women, and those patients who have multiple co-morbid conditions. All these concerns have to be addressed so that these drugs can be utilized in a most optimal fashion for different groups of patients. [28]

5 Emerging Therapies and Combination Approaches

The future of research in obesity pharmacotherapy is moving in the direction of developing new drugs to enhance the efficacy of these drugs. Dual and triple agonists, which act on several metabolic targets, have shown promising results in early clinical trials. These drugs have the potential to increase weight loss and metabolic effects compared to other drugs. The combination of GLP-1 receptor agonists and other anti-obesity drugs has the potential to increase the efficacy of these drugs through synergistic effects [31]

6 Personalized Medicine and Future Directions

The future of obesity therapy is likely to focus on a more personalized medicine approach that will provide a framework for the management of obese patients based on individual needs and metabolic response. There is a possibility that pharmacogenomics and biomarker research may reveal obese patients who are likely to benefit from GLP-1 receptor agonists therapy. The future of better drug delivery systems for GLP-1 receptor agonists, including oral forms and long-acting injectables, is expected to enhance the use of these drugs in obesity therapy in the future. The future of GLP-1 receptor agonists is likely to depend on research and innovation in overcoming the challenges and improving the therapeutic potential of these drugs. [29]

7 Overall Future Outlook

Thus, in summary, although GLP-1 receptor agonists have revolutionized the management of obesity, there are many challenges that are yet to be overcome, and these include cost, safety, and weight maintenance concerns, which are of critical importance if the full benefits of these agents are to be realized in the management of obesity, although research into new therapeutic options is promising in this regard.

Future Perspectives

1 Development of Novel Therapies

The future of the management of obesity is always in flux as more research is being carried out to develop even more potent pharmacological agents for the management of weight loss. The best advancement in the management of obesity is the development of dual and triple agonists, which act on different metabolic pathways. This includes the development of dual and triple agonists with GLP-1, as well as other hormones such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon. The new agents hold the potential to enhance the benefits of weight loss through the improvement of energy expenditure, as well as the reduction of appetite. The new agents hold the potential for the enhancement of weight loss compared to the traditional GLP-1 receptor agonists, which is the best advancement in the future of the management of obesity. [13], [32]

2 Advancements in Drug Delivery Systems

Another important field in the development is the improvement of drug delivery systems to enhance the level of convenience for the patient. As earlier mentioned, the majority of GLP-1 receptor agonists, including Semaglutide, are injected subcutaneously. This may not be very convenient for the patient. Fortunately, recent developments in the field have seen the creation of oral GLP-1 receptor agonists. An example is oral semaglutide, which is non-invasive and can serve as an alternative to the injected forms. This is likely to enhance compliance with the medication and the availability of treatment options for the patient. Further research is being carried out to ensure the creation of drug formulations with a longer half-life, which does not require frequent injections [33]

3 Personalized Medicine Approach

The concept of personalized medicine is increasing in importance in the treatment of obesity. The response to GLP-1 receptor agonists may vary from person to person based on genetic, metabolic, and lifestyle variations. It is thought that in the future, greater emphasis will be placed on the discovery of biomarkers and other personalized variables to assess the response to these medications, which will aid in the better treatment of obese patients. This will aid in selecting the most appropriate medication for the patient so that not only will the benefits be maximized but also the side effects will be kept to a minimum [32], [34]

4 Long-Term Safety and Real-World Evidence

In spite of the availability of evidence regarding the safety and efficacy of these medications, further research is needed to assess the long-term effects of these medications, especially in non-diabetic patients. The real-world evidence will play an important role in understanding the long-term safety, efficacy, and quality of life associated with these medications in various patients. Further, the long-term effects of these medications will help in understanding the unusual effects of these medications, which might not be observed in the trials. The evidence will help in boosting the confidence regarding the use of these medications, which will eventually result in the increased use of these medications. [32], [33]

5 Expanding Therapeutic Applications

Other than these two medical conditions, there are other medical conditions for which GLP-1 receptor agonists show promise in terms of their potential benefits. New studies have shown that these GLP-1 receptor agonists have the potential to treat other medical conditions such as cardiovascular diseases, non-alcoholic fatty liver diseases, and even neurological diseases because of their anti-inflammatory properties. It can thus be said that the science behind these GLP-1 receptor agonists will add to their importance. [33]

Summary

As a brief conclusion, it can be said that the future of GLP-1 receptor agonist therapy in obesity management looks very bright. Improved drug development, improved drug delivery systems, and the use of a more "personalized medicine" approach will help in improving the results of the therapy in the future. Moreover, future research on these drugs in terms of safety profiles and new uses will also have a significant impact on the use of these drugs in obesity management. All these trends in GLP-1 receptor agonist therapy point to a very bright future for these drugs in obesity management.

Conclusion

It is a complex and chronic metabolic disorder, which is still one of the major health challenges in the world and hence requires the development of effective therapeutic strategies in the management of the disorder. Even though the traditional therapeutic strategies, such as lifestyle modification and traditional pharmacotherapy, have been used in the management of obesity, they have shown poor therapeutic outcomes in the long term. Therefore, the development of advanced therapeutic strategies is urgently required. The GLP-1 receptor agonists are still one of the major breakthroughs in the management of obesity, especially in non-diabetic patients.

Agents like these, especially Semaglutide, have shown promising potential in the induction of weight loss to a significant extent through various mechanisms, including the reduction of appetite, delayed gastric emptying, and metabolic control. In this context, the STEP program has shown promising results in the induction of weight loss with the improvement of cardiometabolic risk factors. GLP-1 receptor agonists, compared to other anti-obesity medications, show the best outcome in terms of efficacy and sustainability, making them the first choice in the current pharmacotherapy of obesity. [13]

This implies that apart from their effectiveness, these drugs are also safe for use by patients. In addition, the side effects, which are minimal, are not long-term. It is worth noting, however, that despite the fact that there is a minimal risk of hypoglycemia in non-diabetic patients, these drugs are very significant, especially in relation to their benefits on cardiovascular conditions. The challenges associated with these drugs include their cost, their long-term effects, and the fact that if patients stop using these drugs, they will gain weight..

Looking into the future, the prospects for the management of obesity are bright with the introduction of newer agents and combination therapies, which act on different pathways. Advances in the field of personalized medicine and drug delivery systems will add to the success of this therapy. Further studies are needed to assess the long-term safety, dosing regimens, and availability of these therapies.

In conclusion, the role of GLP-1 receptor agonists has been demonstrated as an effective and innovative approach to the management of obesity among non-diabetic patients. The potential of these agents to induce significant weight loss among obese patients makes them the cornerstone of the evolving armamentarium for the management of obesity. With further developments and accessibility to these agents, the role of GLP-1 receptor agonists is potentially capable of alleviating the global epidemic of obesity.

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